

REMARKS**I. The Subject Matter of the Claims**

In general, the subject matter of the claims relates to methods for reducing tumor mass in an individual suffering from cancer by administering to the individual a modified herpes virus with a mutation that prevents expression of one $\gamma_134.5$ gene product and is a cancer therapeutic. Upon entry of the present amendment, pending claims in the application read as set out in Appendix A hereto.

II. The Amendment to the Claims

Claim 1 is amended to recite that methods of the invention reduce tumor mass as disclosed in the specification at page 8, lines 11 through 20. Attached as Appendix B is a marked-up version of the changes made to claims by the amendment. Appendix B is captioned "**Version with markings to show changes made**".

III. The Outstanding Rejections

Claims 1 through 9 were rejected under 35 USC §112, first paragraph, for assertedly lacking enablement.

Claims 1 through 9 were rejected under 35 USC §102(b) for assertedly being anticipated by the disclosure of Martuzza, et al., US Patent 5,585,096 [hereinafter Martuzza]. Claims 1-5, 7 and 9 were further rejected for allegedly being anticipated by the disclosure of Advani et al., Gene Therapy 5:160-165 (1998) [hereinafter Advani 1998] or Advani et al., J. Rad. Oncol. Biol. Phys. 39(2 Supp):251 (1997) [hereinafter Advani 1997].

Claims 1 through 9 were also rejected under 35 USC §112, second paragraph for assertedly being indefinite.

IV. Patentability Arguments

1. The Rejection under §112, First Paragraph

Claims 1 through 9 were rejected under 35 USC §112, first paragraph, for assertedly lacking enablement. Specifically, the examiner argued that (i) gene therapy was unpredictable at the time the application was filed, (ii) the claims read on killing any cancer cells, and (iii) guidance in the specification for practice of the invention is insufficient thereby requiring undue experimentation. The applicants respectfully disagree.

As a preliminary comment, the examiner's categorization of the present invention as "gene therapy" requires a broad interpretation of this term. The examiner relies on the disclosure of Verma (1997) to describe problems associated with gene therapy, but the therapeutic intervention described in Verma is clearly distinct from the present invention. In the abstract, Verma defines gene therapy in "simple" terms as "putting *corrective* genetic material into cells" and at page 239, first paragraph, Verma states that one of the problems with this method is the "lack of sustained [gene] expression." The Verma gene therapy methods are clearly intended to introduce a specific protein-coding DNA into a cell [which presumably expresses the specifically encoded protein at an aberrant level], have the DNA integrate into the cellular genome, and provide *sustained expression* of the encoded protein in the target cell resulting in the desired therapeutic effect. Methods of this type are designed to circumvent the need for administering a therapeutic protein by providing cells with the means to make the protein. The present methods are distinct.

First, there is no *corrective* DNA being introduced. All DNA being administered is viral, and its administration is not intended to repair or replace a human protein-coding DNA. Second, *sustained* expression (as defined by Verma) is not an intended result from the present methods. Indeed, ~~expression cannot be sustained because the desired~~ result is death of the target cell, and this result represents yet a third difference from the methods described in Verma.

Regarding the examiner's reliance on the disclosure of Crystal (1995), the applicants submit that the nude mouse cancer model is well known and routinely utilized by those of ordinary skill in the art as evidenced by the attached exhibits. In *Research Animal*

Review Vol.1, No. 2, March 1996¹, last paragraph at page 1, it is unambiguously stated that nude mice are "widely utilized in evaluating anticancer agents prior to human clinical trials" [Exhibit A] and the American Federation for Aging Research (AFAR)² proclaims mice to be "excellent models for cancer research." [Exhibit B] The nexus between results obtained in mouse models and subsequently successful human therapy is found in an article in the Orlando Sentinel on April 7, 2002 by Frank Trull³ from the Foundation for Biomedical Research, which states that "many diseases that once killed millions of people every year are either treatable or have been eradicated altogether" thanks to animal research, and in particular, the nude mouse which "has become an incredibly important model for understanding cancer suppression" [Exhibit C]. That mouse models are accepted in the art is further evidenced by the fact that Jackson Laboratory⁴ offers 427 different mouse strains specifically bred for cancer research [Exhibit D]⁵.

Regarding the examiner's first reliance on Advani (1998), the applicant notes that, despite comments in the reference, the disclosure in the specification make it explicitly clear that the methods as claimed do in fact work. Example 2 at page 7 demonstrates that xenograft tumors arising from epidermal carcinoma cells (page 8, lines 11-16), prostate adenocarcinoma cells (page 8, line 17-18) and hepatoma adenocarcinoma cells (page 8, lines 19-20) all exhibited reduced tumor volume using the methods as claimed. The fact that three distinct tumor types were significantly reduced in mass supports the breadth of the claims in reciting treating cancer in general.

With further regard to comments in Verma (1997) about the possible effect of an immune response against a viral agent, the applicant notes that the dosage of any drug must be formulated with the expectation that it will be cleared from circulation, for example, via the reticuloendothelial system, and as a result, the circulatory half life is generally proportional to the amount of drug administered. The Verma disclosure is therefore irrelevant to the method as claimed because it is a statement of the obvious with respect to therapeutics in general though applied to viral vectors of the present methods.

¹ <http://www.taconic.com/newsletters/march96/march96b.htm>

² <http://www.infoaging.org/b-ami-9-cancer.html>

³ http://www.mofed.org/Animal_Research.htm

⁴ <http://jaxmice.jax.org/html/pricelist/modelspdf.shtml>

The examiner's reliance on the disclosure of Chamber (1995) is unclear. To the extent that this reference is cited for its description of the need to permit and still control $\gamma_134.5$ gene expression, the applicants submit that the method for effecting mutation of a single copy of the gene so as to achieve the desired result with minimal deleterious side effects can be determined using an appropriate model system. The person of ordinary skill in the art would be expected to be aware of the options available and know how they can be applied to achieve the optimal effect. Moreover, practice of the claims methods would not require undue experimentation because the specifications teaches how to effectively utilize the disclosed mouse model, and evaluate results from the model, to effectively optimize parameters for human administration. As noted in the Exhibits, this type of preparative experimentation is common in the art in view of the wide spread acceptance of animal, and mouse, models in general, and the guidance in the specification reduces the degree of experimentation to nothing more than routine.

Finally, regarding the examiner's position that the specification fails to provide guidance with respect to different HSV mutants and different methods of administration, the applicant submits that the specification demonstrates an operative aspect of the invention against which all alternative aspect can be compared. Optimizing various parameters can therefore be effected using the exemplified method as a positive control. Such optimization is certainly routine in the art and not undue.

The applicants submit that the invention is demonstrated in the specification to work, the disclosure in its entirety supports the breadth of the claims, and the guidance therein eliminates the need for undue experimentation. Accordingly, the rejection of claims under section 112 may properly be withdrawn.

2. The Rejections under §102(b)

The examiner rejected claims 1 through 9 for assertedly being anticipated by the disclosure of Martuzza and claims 1 through 5, 7 and 9 for assertedly being anticipated by the disclosures of Advani 1997 or Advani 1998. The applicants respectfully disagree.

⁵ Jackson Laboratory publishes a newsletter providing information relating to use of their mouse strains in biological and biomedical research at <http://jaxmice.jax.org/html/jaxnotes/JAXNoteIndex.shtml>.

Martuzza describes treatment of tumors using HSV mutants that lack *both* copies of the $\gamma 1.34.5$ gene and is therefore outside the scope of the methods as claimed. As expressly recited, the HSV mutant utilized in the claimed methods have one functional $\gamma 1.34.5$ gene and nothing in Martuzza suggests use of this type of mutant.

Advani 1997 and 1998 disclose the same data as found in Figure 3 of Advani 1998, but neither reference discloses that the R7020 virus is able to kill tumor cells at a rate that is greater than the tumor is able to grow which is necessary to result in reduced tumor mass.

Because anticipation requires that every limitation of the claims be found in the cited art, neither Martuzza nor the Advani references can anticipate the claimed invention and the rejections must be withdrawn.

3. The Rejections under §112, Second Paragraph

The examiner rejected claim 1 (and all claims depending from claim 1) for reciting "an individual" which the examiner believed rendered the claim indefinite. Claim 5 was also rejected for reciting the term "unique region" which the examiner felt was not clearly defined.

Regarding the first rejection, the applicants submit that the term "individual" embraces any patient in need of treatment to retard or reduce tumor growth as disclosed in the specification at page 4, lines 4 through 6. Accordingly, the term is not indefinite and the rejection may properly be withdrawn.

Regarding the second rejection, the applicant submits that the "unique" regions of the HSV genome are well-recognized by one of ordinary skill in the art as evidenced by the description provided in Exhibit E⁶. As indicated in this description, the art recognizes a "long unique regions" and a "short unique region." The limitation in the claim that the HSV mutant used in the method further comprises an alteration in "a unique region" indicates that in the methods, the HSV mutant may be further modified in either of these two regions. In

⁶ <http://darwin.bio.uci.edu/~faculty/wagner/hsv3f.html>

view of the evidenced understanding of this term in the art, the rejection may properly be withdrawn.

SUMMARY

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue.

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Respectfully submitted,

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Version With Markings to Show Changes Made

1. A method for [killing cancer cells] reducing tumor mass comprising the step of administering to an individual suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that one $\gamma 1.34.5$ gene remains intact and said amount of HSV being effective to [kill cancer cells] reduce tumor mass.

APPENDIX A

1. A method for reducing tumor mass comprising the step of administering to an individual suffering from cancer an amount of a Herpes simplex virus (HSV) comprising a modified HSV genome wherein said modification comprises a modification of an inverted repeat region of said HSV genome such that one *₁34.5 gene remains intact and said amount of HSV being effective to reduce tumor mass.

2. The method of claim 1 wherein the modification of the inverted repeat region of the genome comprises an alteration of a copy of a *₁34.5 gene which renders that copy of the gene incapable of expressing an active gene product.

3. The method of claim 2 wherein the alteration of the *₁34.5 gene comprises an insertion of a DNA sequence comprising one or more nucleotides into the coding region or regulatory region of the gene.

4. The method of claim 2 wherein the alteration of the *₁34.5 gene comprises a deletion of all or part of the coding region or regulatory region of the gene.

5. The method of claim 1, 2, 3, or 4 wherein the modified HSV genome further comprises an alteration in a unique region of the HSV genome.

6. The method of claims 1, 2, 3, or 4 wherein the cancer is a noncentral nervous system cancer.

7. The method of claim 1, 2, 3, or 4 wherein the cancer is a central nervous system cancer.

8. The method of claim 5 wherein the cancer is non-central nervous system cancer.

9. The method of claim 5 wherein the cancer is a central nervous system cancer.